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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte JOAN D. LEONARD and ROBERT W. TULLY

Appeal 2009-013864[1]
Application 09/708,352
Technology Center 1600

Before ERIC GRIMES, FRANCISCO C. PRATS, and
JEFFREY N. FREDMAN, *Administrative Patent Judges*.

PRATS, *Administrative Patent Judge*.

DECISION ON APPEAL[2]

This appeal under 35 U.S.C. § 134 involves claims to vaccines that protect against diseases caused by *Mycoplasma bovis*. The Examiner rejected the claims as anticipated and obvious.

We have jurisdiction under 35 U.S.C. § 6(b). We affirm-in-part.

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[1] Oral argument was heard in this appeal on September 14, 2010.
[2] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, or for filing a request for rehearing, as recited in 37 C.F.R. § 41.52, begins to run from the "MAIL DATE" (paper delivery mode) or the "NOTIFICATION DATE" (electronic delivery mode) shown on the PTOL-90A cover letter attached to this decision.

STATEMENT OF THE CASE

"Clinical disease and losses associated with infections caused by *Mycoplasma bovis* in beef and dairy cattle include: contagious mastitis, respiratory pneumonia, joint infections (arthritic conditions), keratoconjunctivitis, and middle ear infections" (Spec. 1).

Claims 1, 3-12, and 29-56 are pending and on appeal (App. Br. 5).[3] Claims 1, 5, 8, and 29 illustrate the appealed subject matter and read as follows:

> 1. A vaccine which is protective against *Mycoplasma bovis* clinical disease in a bovine species comprising at least one inactivated or attenuated *Mycoplasma bovis* biotype, an adjuvant, and a pharmaceutically acceptable excipient, and wherein the adjuvant does not include saponin and the clinical disease includes respiratory pneumonia.
>
> 5. A vaccine which is protective against *Mycoplasma bovis* clinical disease in a bovine species comprising at least one inactivated or attenuated *Mycoplasma bovis* biotype, an adjuvant, and a pharmaceutically acceptable excipient, wherein at least one of the inactivated or attenuated *Mycoplasma bovis* biotypes is selected from the group consisting of biotype A, biotype B and Biotype C, and wherein the adjuvant does not include saponin.
>
> 8. A vaccine which is protective against *Mycoplasma bovis* clinical disease in a bovine species comprising at least two inactivated or attenuated *Mycoplasma bovis* biotypes and a pharmaceutically acceptable excipient.
>
> 29. A vaccine which is protective against *Mycoplasma bovis* mastitis in a bovine species comprising at least one inactivated

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[3] Amended Appeal Brief filed March 7, 2008.

or attenuated Mycoplasma *bovis* biotype and a pharmaceutically acceptable excipient.

The Examiner cites the following documents as evidence of unpatentability:

John Thayer Boothby, Immunologic Responses to *Mycoplasma bovis* (1982) (Ph.D. dissertation on file with University Microfilms International) ("Boothby I").

F. Poumarat et al., *Genomic, protein and antigenic variability of mycoplasma bovis*, 40 VETERINARY MICROBIOLOGY 305-321 (1994).

C.J. Thorns and E. Boughton, *Effect of serial passages through liquid medium on the virulence of Mycoplasma bovis for the mouse mammary gland*, 29 RESEARCH IN VETERINARY SCIENCE 328-332 (1980).

The following rejections are before us for review:

(1) Claims 1, 3, 5, 6, 29, 30, 40-44, and 52-55, rejected under 35 U.S.C. § 102(b) as anticipated by Boothby I (Ans. 3-5);

(2) Claims 1, 3-12, and 29-56, rejected under 35 U.S.C. § 103(a) as obvious over Boothby I, Poumarat, and Thorns (Ans. 5-9).

ANTICIPATION

ISSUE

The Examiner cites Boothby I as disclosing vaccine compositions that contain killed *M. bovis* (Ans. 4). The Examiner also notes Boothby I's disclosure that, once vaccinated with the composition, "there was no sign of respiratory illness in any calves used in the study (page 136). Therefore, the vaccines were protective against respiratory infection caused by *M. bovis*" (*id.* at 5).

Appellants argue the claims subject to this rejection separately (*see* App. Br. 11-14). Specifically, with respect to all of the rejected claims, Appellants contend that the absence of unfavorable reactions resulting from the claimed vaccine, contrasted with the unfavorable delayed hypersensitivity caused by Boothby I's vaccine, "is a real difference between the Appellants' vaccine and Boothby I" (*id.* at 11).

Regarding claims 5, 6, and 54, Appellants argue that Boothby I does not disclose that the vaccine contains at least one of *M. bovis* biotypes A, B, or C, as those claims require (*id.* at 12). Regarding claims 29, 30, and 40-44, Appellants argue that the evidence of record does not support a finding that Boothby I's vaccine is protective against mastitis (*id.* at 12-14; *see also* Reply Br. 6-11).

We select claims 1, 5, and 29 as representative of the rejected claims. *See* 37 C.F.R. § 41.37(c)(1)(vii).

Thus, in view of the positions advanced by Appellants and the Examiner, the issue with respect to this rejection is whether the evidence of record supports the Examiner's position that Boothby I describes an *M. bovis* vaccine that has all of the features required by claims 1, 5, and 29.

FINDINGS OF FACT ("FF")

Specification

1. The Specification discloses using PCR fingerprinting to differentiate field isolates and strains of *M. bovis* into various biotypes designated as A, B, and C (Spec. 12-13).

2. Thus, *M. bovis* DNA is isolated and amplified using primers with the sequences in SEQ ID NO: 1 and SEQ ID NO: 2, and is then electrophoresed on an agarose gel, the gel showing different banding patterns characteristic

of the three biotypes, A, B, and C, identified by Appellants (*id.*; *see also* Figures 1 and 2 (showing characteristic bands of biotypes A, B, and C on agarose gels)).

3. The Specification does not disclose that the *M. bovis* strain California 201 was among the strains tested for biotype (*see id.* at 13).

4. The Specification states that the "term 'biotype' means a variant of a species, i.e. a strain, that can be distinguished by one or more characteristics, such as ribosomal RNA sequence variation, DNA polymorphisms, serological typing, or toxin production" (*id.* at 5).

Boothby I

5. Boothby I studied "the effect of systemic and respiratory administration of killed M bovis antigen in combination with various adjuvants on the immune responses of calves to vaccination, and to experimental challenge exposure with live M bovis in the nares and bronchio-alveolar region (BAR)" (Boothby I 129-130).

6. In the study, Boothby I vaccinated 15 calves with various preparations of the *M. bovis* strain California 201 (*id.* at 131): "[t]hree animals were vaccinated with killed M bovis in phosphate buffered saline solution (PBSS), and the remaining 12 were vaccinated with the same antigen in combination with one of 4 adjuvant preparations (3 calves per experimental group)" (*id.* at 130).

7. Boothby I's vaccine compositions contained formalin-killed *M. bovis* cells as the antigen in the following formulations:

> Preparations for systemic immunization consisted of 0.5 ml antigen, 1.0 ml Freunds Incomplete Adjuvant and 0.5 ml of one of the following in aqueous solution: 10.0 mg N-

> acetylmuramyl-L-alanyl-D-isoglutamine (MDP), 5.0 mg Amphotericin B (Am-B), 500 mg of combined magnesium/ aluminum hydroxide with 2 x 10^{10} killed Bordetella pertussis (Bp). The other experimental groups received the same antigen in Freunds incomplete adjuvant alone (FIA) or in PBSS without adjuvant. Vaccine preparations for intranasal and intratracheal immunization were the same as those used for systemic immunization except that the oil phase (FIA) and magnesium/aluminum hydroxide were omitted, and the total volume was adjusted to 15 mls with PBSS.

(*Id.* at 131 (citations omitted).)

8. Boothby I summarizes its results as follows:

> The adjuvant preparations elicited strong systemic antibody responses compared to those measured in calves not given adjuvant. Most calves given adjuvants responded to vaccination in the respiratory tract with a strong IgA response, but these responses were not above those of calves given M bovis antigen without adjuvant. Calves given some adjuvants developed strong delayed-type hypersensitivity responses compared to calves given M bovis without adjuvant as measured by skin test, but none of the calves developed a strong cellular response as measured by lymphocyte stimulation.

(*Id.* at 128.)

9. Boothby I notes that, "[s]ince none of the calves in the present study showed any signs of respiratory illness although a wide range of immune responses were observed, there must be a wide range of acceptable responses to M bovis infection as previously observed" (*id.* at 136).

10. Boothby I also notes that "[a]ll groups receiving adjuvant preparations developed delayed-type hypersensitivity at 14 weeks as determined by increase in skinfold thickness at 72 hours" (*id.*).

Poumarat

11. The Examiner cites Poumarat as evidence that the *M. bovis* in Boothby I's vaccines is necessarily one of the claimed biotypes, A, B, or C (Ans. 13).

12. Poumarat describes a study that investigated "the genomic, protein and antigenic variability of *M. bovis*" (Poumarat 306).

13. "Restriction endonuclease analysis (REA) with three enzymes *Sma*I, *Pst*I, *Bam*HI . . . identif[ied] 13 different genomic groups among 37 *Mycoplasma bovis* strains. One genomic group was comprised of 14 strains" (*id.* at 305 (abstract)).

14. Poumarat investigated strains from each of the genomic groups for antigen variability using polyclonal and monoclonal antibodies, and found that the strains' antigenic profiles "differed markedly one from the other, the heterogeneity being equally great among the strains belonging to the same genomic group as those coming from different groups" (*id.*).

Thus, Poumarat concluded, "[t]here appeared to be no relation between the genomic variability of *M. bovis* and the antigenic variability" (*id.* at 318).

15. Poumarat concluded that "[t]wo highly-variable antigenic systems have been identified so far for *M. bovis*, but their in vivo function is not known. It is evident that this antigenic variability must be taken into account in developing diagnostic and vaccination strategies" (*id.* at 319).

Boothby II [4]

16. Appellants cite Boothby II as evidence that Boothby I's vaccines were not protective against mastitis (App. Br. 21-22; Reply Br. 6-9); and the Examiner disputes Appellants' characterization of the reference (Ans. 20).

17. Boothby II investigated the "effect of vaccination on milk production . . . in vaccinated and control cows experimentally challenged in two of four quarters [of their udders] with live *Mycoplasma bovis*" (Boothby II 200 (abstract)).

18. Boothby II's vaccine contained formalin-killed *M. bovis* strain California 201 in Freund's Complete Adjuvant (*id.* at 202).

19. Boothby II discloses that "[a]ll challenged quarters became infected, had strong California Mastitis Test reactions, and had a drastic (> 85%) loss in milk production" (*id.* at 200 (abstract)).

20. Regarding unvaccinated cows, Boothby II discloses that "four of eight challenged quarters on control cows remained infected, had mostly positive California Mastitis Test scores, produced mostly normal-appearing milk, and recovered some productive capabilities" (*id.*).

21. Regarding vaccinated cows, Boothby II discloses that, "[b]y the end of the study no *M. bovis* could be recovered from challenged quarters on vaccinated cows and the milk appeared mostly normal. The California Mastitis Test scores on these quarters, however, remained elevated" (*id.*).

22. Boothby II further notes:

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[4] J.T. Boothby et al., *Experimental Intramammary Inoculation with Mycoplasma bovis in Vaccinated and Unvaccinated Cows: Effect on Milk Production and Milk Quality*, 50 CAN. J. VET. RES. 200-204 (1986).

> All challenged quarters on vaccinated cows remained CMT-positive for the duration of the study while some challenged quarters on control cows became CMT-negative. Among unchallenged quarters, four of eight quarters on vaccinated cows and three of eight quarters on control cows developed CMT reactivity, but most became CMT-negative by the end of the study.

(*Id.* at 202-203.)

PRINCIPLES OF LAW

As stated in *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992):

> [T]he examiner bears the initial burden . . . of presenting a *prima facie* case of unpatentability. . . .
>
> After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of evidence with due consideration to persuasiveness of argument.

"To anticipate a claim, a prior art reference must disclose every limitation of the claimed invention, either explicitly or inherently." *In re Schreiber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997).

As stated in *In re Best*, 562 F.2d 1252, 1254-1255 (CCPA 1977) (quoting *In re Swinehart*, 439 F.2d 210, 212-13 (CCPA 1971)):

> [W]here the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, it possesses the authority to require the applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on.

The examiner cannot, however, establish inherency merely by demonstrating that the asserted limitation is probable or possible. *In re Oelrich*, 666 F.2d 578, 581 (CCPA 1981). Nonetheless, if "the disclosure is

sufficient to show that the natural result flowing from the operation as taught would result in the performance of the questioned function, it seems to be well settled that the disclosure should be regarded as sufficient." *Id.* (quoting *Hansgirg v. Kemmer*, 102 F.2d 212, 214 (CCPA 1939)).

ANALYSIS

A preponderance of the evidence supports the Examiner's finding that Boothby I anticipates claim 1. Claim 1 recites a vaccine which is protective against *Mycoplasma bovis* respiratory pneumonia in a bovine species. The vaccine must contain at least one inactivated or attenuated *M. bovis* biotype, an adjuvant that does not contain saponin, and a pharmaceutically acceptable excipient.

As the Examiner points out, Boothby I discloses vaccines that contain formalin-killed *M. bovis*, combined with any one of several adjuvants which Appellants do not dispute lack saponin, and the pharmaceutically acceptable excipient water (FF 7). As the Examiner also points out, the vaccines elicited strong antibody responses, and none of the vaccinated calves in the study showed any signs of respiratory illness, despite having been experimentally challenged in the nares and bronchio-alveolar regions with live *M. bovis* (FF 5, 8, 9).

Thus, the Examiner has provided evidence that Boothby I's vaccine not only contains the ingredients required by claim 1, but also meets claim 1's functional limitation requiring protection against respiratory pneumonia. In contrast, while Appellants urge that the Examiner has failed to adequately explain why Boothby I meets the functional limitation in claim 1 (*see* Reply Br. 2-6), Appellants provide no specific reasoning or evidence that undermines the reasonableness of the Examiner's fact-based finding.

Rather, Appellants argue only that the hypersensitivity resulting from Boothby I's vaccine (FF 10) demonstrates that Boothby I's vaccine is different than the vaccine recited in claim 1 (App. Br. 11). Claim 1 does not, however, recite any limitation that excludes vaccines which result in hypersensitivity. Thus, as Appellants' argument is not directed to a limitation present in claim 1, Appellants' argument is not persuasive of that claim's patentability.

In sum, a preponderance of the evidence supports the Examiner's finding that Boothby I anticipates claim 1. We therefore affirm the Examiner's anticipation rejection of that claim over Boothby I, as well as claims 3, 52, 53, and 55, which were not argued separately. *See* 37 C.F.R. § 41.37(c)(1)(vii).

We agree with Appellants, however, that the Examiner has not shown that Boothby I's vaccine inherently contains at least one inactivated *M. bovis* biotype selected from biotypes A, B, and C, as recited in claim 5. As noted above, biotypes A, B, and C are identified by a specific PCR fingerprinting method prescribed in the Specification (FF 1, 2).

As also noted above, no evidence is presented by the Examiner that any of the strains identified as having biotypes A, B, or C was the California 201 strain used in Boothby I's vaccine (FF 3). As further noted above, Poumarat discloses that restriction endonuclease analysis of *M. bovis* DNA identified 13 different genomic groups among 37 *M. bovis* strains (FF 13).

The Examiner urges that Poumarat demonstrates that Boothby I's strain is one of the biotypes recited in claim 5 (Ans. 13). However, given the potential number of *M. bovis* genomic groups to which Boothby I's strain might belong (at least 13), and given that California 201 is not among

the strains of record that fall within the claimed biotypes, we are not persuaded that an ordinary artisan would have concluded that Boothby I's *M. bovis* strain necessarily falls within biotypes A, B, or C.

In sum, because the preponderance of the evidence does not support the Examiner's finding that Boothby I's vaccine necessarily contains one of the biotypes recited in claim 5, we reverse the Examiner's anticipation rejection of that claim, and its dependent claims 6 and 54, over Boothby I.

We also agree with Appellants that a preponderance of the evidence does not support the Examiner's finding that Boothby I's vaccine is inherently protective against *M. bovis* mastitis in a bovine species, as recited in claim 29. We note, as the Examiner argues, that Boothby II discloses that a vaccine containing formalin-killed California 201, the same *M. bovis* strain used in Boothby I, resulted in no *M. bovis* being recoverable from quarters challenged with live *M. bovis* (*see* FF 21).

However, as Appellants point out, the California Mastitis Test (CMT) scores on all vaccinated quarters remained elevated throughout the duration of Boothby II's study (*id.*). In contrast, as noted above, some challenged quarters on control, i.e. unvaccinated, cows became CMT-negative (FF 22).

Thus, even if we assume that the Examiner has made a prima facie case of anticipation by showing that Boothby I's vaccine contains the same species of organism, Boothby II shows that essentially the same vaccine as in Boothby I did not protect cows against mastitis as measured by the CMT test, and as compared to controls.

As noted above, inherency cannot be established by probability or possibility. *In re Oelrich*, 666 F.2d at 581. Given the results presented in Boothby II, we agree with Appellants that a preponderance of the evidence

does not show that the vaccine in Boothby I inherently protects against *M. bovis* mastitis in a bovine species, as required by claim 29. Accordingly, we reverse the Examiner's rejection of that claim, and its dependent claims 30 and 40-44, as anticipated by Boothby I.

OBVIOUSNESS

ISSUE

Claims 1, 3-12, and 29-56 stand rejected under 35 U.S.C. § 103(a) as obvious over Boothby I, Poumarat, and Thorns (Ans. 5-9). The Examiner cites Boothby I for its disclosure of a vaccine containing inactivated *M. bovis*, but concedes that Boothby I does not include more than one biotype in its vaccine (Ans. 7-8).

The Examiner reasons that an ordinary artisan would nonetheless have considered it obvious to include more than one biotype in Boothby I's vaccine in view of Poumarat's teaching of a "marked intraspecies genomic heterogeneity among isolates of *Mycoplasma bovis* collected from different geographic origins and that antigenic variability must be taken into account in developing diagnostic and vaccination strategies" (*id.* at 9).

The Examiner further reasons that an ordinary artisan would have considered it obvious to use attenuated *M. bovis* biotypes in Boothby I's vaccine in view of Thorns' teaching that "high passaged *M. bovis* strains were less virulent and produced only minor histopathological changes in vaccinated animals and do not cause systematic changes in inoculated animals" (*id.*).

Appellants argue the claims subject to this rejection separately (*see* App. Br. 18-22). Specifically, with respect to all of the rejected claims, Appellants contend that the absence of unfavorable reactions resulting from

the claimed vaccine, contrasted with the unfavorable delayed hypersensitivity caused by Boothby I's vaccine, and the undesirable histopathological changes caused by Thorns' preparation, demonstrates that the cited references do not support a prima facie case of obviousness (*id.* at 18).

Regarding claims 8-12, 31-39, and 46-51, Appellants argue that the cited references do not suggest including more than one biotype in an *M. bovis* vaccine because Poumarat teaches that the same degree of variability exists within genomic groups as across them (*id.* at 19). Thus, Appellants urge, because "Poumarat teaches that there would be no gain in antigenic variability from including more than one type of *Mycoplasma bovis* in a vaccine . . . there would be no point in having more than one type of *Mycoplasma bovis* in a vaccine" (*id.*). Appellants urge that Poumarat therefore "teaches away from the invention defined by claims 8-12, 31-39, and 46-51" (*id.*).

Regarding claims 29, 30, and 40-45, Appellants argue that none of the cited references teach or suggest preparing a vaccine that is protective against *M. bovis* mastitis (*id.* at 20-21). Specifically, Appellants argue, the evidence of record shows that there was a long-felt need for a vaccine against bovine *M. bovis* mastitis, which others had tried and failed to fulfill

(*id.* at 21-22 (citing Hanson I,[5] Hanson II,[6] and Boothby II); *see also* Reply Br. 10-11 (citing Heller[7])).

Regarding claims 34-39 and 46-51, Appellants note that these claims "require that the at least two biotypes be genetically different, as judged by analysis of DNA or RNA" (App. Br. 20). Given Poumarat's express teaching that genetic differences are irrelevant with respect to antigenicity, Appellants argue, an ordinary artisan "would clearly interpret this conclusion as a teaching that nothing is to be gained from including biotypes that are genetically different in a vaccine, and thus would be discouraged from the invention of claims 34-39 and 46-51" (*id.*).

Regarding claim 56, Appellants argue that, "although Thorns does disclose attenuated strains of *Mycoplasma bovis*, Thorns states that these strains are not vaccines, but might provide 'further insight' which could 'perhaps' lead to the development of a vaccine" (*id.* at 22 (citing Thorns 332)). Thus, Appellants conclude, given the absence of "disclosure of an attenuated vaccine that is protective against respiratory pneumonia in any of Boothby I, Thorns, or Poumarat, and the lack of any suggestion as to how such a vaccine could be produced in those references, it cannot properly be said that those references make obvious claim 56" (*id.*).

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[5] Maureen Hanson, *Mycoplasma mastitis: It's everyone's problem*, BOVINE VETERINARIAN 4-8 (September 2001).
[6] Maureen Hanson, *Mycoplasma mastitis: Prevention and control*, BOVINE VETERINARIAN 12-20 (October 2001).
[7] Martin Heller et al., *Antigen capture ELISA using a monoclonal antibody for the detection of Mycoplasma bovis in milk*, 37 VETERINARY MICROBIOLOGY 127-133 (1993).

We select claims 1, 8, 29, 34, and 56 as representative of the rejected claims. *See* 37 C.F.R. § 41.37(c)(1)(vii).

Thus, in view of the positions advanced by Appellants and the Examiner, the issue with respect to this rejection is whether the evidence of record supports the Examiner's position that an ordinary artisan would have found claims 1, 8, 29, 34, and 56 prima facie obvious in view of Boothby I, Poumarat, and Thorns.

FINDINGS OF FACT

23. Thorns discloses a study in which the "mouse mastitis model was used to examine strains of *Mycoplasma bovis.* Strains that had been passaged in liquid medium more than 60 times were markedly less virulent than the same or different strains with fewer passages" (Thorns 328 (abstract)).

24. "Whereas the low passage strains produced a systemic response in some mice and severe pathological and histopathological changes in the mammary glands of all, the high passage strains produced only minor histopathological changes" (*id.*).

25. Based on its results, Thorns concludes that "[w]hatever mechanisms the virulent strains have lost or modified, they should provide further insight into the pathogenesis of *M bovis* mastitis which could perhaps lead to a stable vaccine for this disease" (*id.* at 332).

PRINCIPLES OF LAW

As the Supreme Court pointed out in *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), when determining whether the prior art supplied a reason for practicing the claimed subject matter, the analysis "need not seek out precise teachings directed to the specific subject matter of the challenged

claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at 418; *see also id.* at 421 ("A person of ordinary skill is . . . a person of ordinary creativity, not an automaton.").

The Court also reaffirmed that prima facie obviousness requires a reasonable expectation of success:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. *If this leads to the anticipated success*, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

Id. at 421 (emphasis added).

ANALYSIS

Appellants' arguments do not persuade us that the Examiner failed to make a prima facie case of obviousness with respect to claim 1.

As discussed above, claim 1 does not contain any language that excludes vaccines that might have undesired side effects, such as the hypersensitivity or minor histopathological changes exhibited, respectively, by the preparations described in Boothby I and Thorns (FF 10, 24). Thus, because Appellants' argument is not directed to a limitation present in the claim, the argument is not persuasive of the claim's patentability.

As also discussed above, Boothby I's vaccines elicited strong antibody responses, and none of the vaccinated calves in Boothby I's study showed any signs of respiratory illness, despite having been experimentally challenged in the nares and bronchio-alveolar regions with live *M. bovis* (FF

5, 8, 9), thus providing evidence that Boothby I's vaccine not only contains the ingredients required by claim 1, but also meets claim 1's functional limitation requiring protection against respiratory pneumonia.

As Appellants point to no clear or direct evidence controverting the reasonableness of the Examiner's conclusion of obviousness with respect to claim 1, we affirm the Examiner's obviousness rejection of that claim over Boothby I, Poumarat, and Thorns. As they were not argued separately, claims 3-7 and 52-55 fall with claim 1. *See* 37 C.F.R. § 41.37(c)(1)(vii).

Claim 8 recites a vaccine which is protective against any *Mycoplasma bovis* clinical disease in a bovine species. The vaccine must contain at least two inactivated or attenuated *M. bovis* biotypes and a pharmaceutically acceptable excipient.

As noted above, the Specification defines biotype as "a variant of a species, i.e. a strain, that can be distinguished by one or more characteristics, such a ribosomal RNA sequence variation, DNA polymorphisms, serological typing, or toxin production" (Spec. 5 (FF 4)).

Thus, because biotypes can be differentiated by serological typing, claim 8 encompasses a vaccine that contains at least two strains of *M. bovis* that have different antigens as determined through immunological testing. As noted above, Poumarat found through immunological testing that *M. bovis* has "[t]wo highly-variable antigenic systems. . . . It is evident that this antigenic variability must be taken into account in developing diagnostic and vaccination strategies" (Poumarat 319 (FF 15)).

Given the high degree of antigenic variability in *M. bovis*, and Poumarat's express teaching that this variability must be taken into account when developing vaccination strategies, we agree with the Examiner that an

ordinary artisan would have been prompted by Poumarat to include more than one *M. bovis* biotype in Boothby I's vaccine, so as to ensure protection against more than just one strain.

We acknowledge Poumarat's disclosure that the antigenic variability in *M. bovis* detected in its investigation was not linked to the genomic groups the study identified (FF 14). As discussed above, however, claim 8 encompasses compositions in which the two biotypes are distinguishable by serological testing. Given the teachings in Poumarat, discussed above, we are not persuaded that an ordinary artisan lacked impetus for combining two serologically different biotypes in an *M. bovis* vaccine.

As Appellants' arguments do not persuade us that the Examiner failed to make a prima facie case of obviousness with respect to claim 8, we affirm the Examiner's rejection of that claim over Boothby I, Poumarat, and Thorns, as well as claims 9-12, 31, and 32, which were argued in the same group as claim 8, and which were not argued separately elsewhere. *See* 37 C.F.R. § 41.37(c)(1)(vii).

Claim 34 recites "[t]he vaccine of claim 8 wherein the at least two inactivated or attenuated *Mycoplasma bovis* biotypes are genetically different as determined by an analysis of DNA or RNA from the biotypes."

We again acknowledge Poumarat's disclosure that the antigenic variability in *M. bovis* detected in its investigation was not directly linked to the genomic groups it identified (FF 14). We are not persuaded, however, that an ordinary artisan would have reasonably inferred from this teaching that nothing would be gained from including genetically different strains in an *M. bovis* vaccine, as Appellants argue (App. Br. 20).

Rather, in our view, an ordinary artisan would have reasonably expected that differences in antigens between *M. bovis* strains would ultimately be reflected in the strains' genetic makeup. Thus, while it might be true that the methods used by Poumarat did not uncover any specific link between the particular genomic groups identified in the study and antigenic variability, given that an ordinary artisan would have expected strains with different antigens to be genetically different, we agree with the Examiner that an ordinary artisan would have been prompted to include genetically different strains, as identified by DNA or RNA analysis, in an *M. bovis* vaccine.

Accordingly, as Appellants' arguments do not persuade us that the Examiner erred in concluding that claim 34 would have been prima facie obvious to an ordinary artisan, we affirm the Examiner's rejection of that claim as obvious over Boothby I, Poumarat, and Thorns, as well as claims 35-39, and 46-51, which were argued with claim 34 (App. Br. 20).

Regarding claim 29, however, we conclude that a preponderance of the evidence does not support the Examiner's position that an ordinary artisan following the teachings of Boothby I, Poumarat, and Thorns would have had a reasonable expectation in producing a vaccine protective against *M. bovis* mastitis in a bovine species. We again note, as the Examiner argues, that Boothby II discloses that a vaccine containing formalin-killed California 201, the same *M. bovis* strain used in Boothby I, resulted in no *M. bovis* being recoverable from quarters challenged, i.e. experimentally infected, with live *M. bovis* (*see* FF 21).

However, as noted above, the California Mastitis Test (CMT) scores on all vaccinated quarters remained elevated throughout the duration of

Boothby II's study (*id.*). In contrast, as also noted above, some challenged quarters on control, i.e. unvaccinated, cows became CMT-negative (FF 22).

Thus, Boothby II shows that essentially the same vaccine as in Boothby I did not protect cows against mastitis as measured by the CMT test, and as compared to controls. Given this disclosure, we are not persuaded that an ordinary artisan following the teachings of Boothby I, Poumarat, and Thorns would have had a reasonable expectation of producing a vaccine capable of protecting against *M. bovis* bovine mastitis.

Accordingly, we find Appellants' arguments persuasive that claims 29, 30, and 40-45 would not have been obvious over Boothby I, Poumarat, and Thorns, and reverse the Examiner's obviousness rejection of those claims.

Claim 56 recites "[a] vaccine which is protective against *Mycoplasma bovis* clinical disease in a bovine species comprising at least one attenuated *Mycoplasma bovis* biotype and a pharmaceutically acceptable excipient, wherein the clinical disease includes respiratory pneumonia."

As discussed above, Boothby I discloses a vaccine containing formalin-killed *M. bovis*, the vaccine being protective against respiratory pneumonia. While Boothby I might not disclose the use of attenuated *M. bovis* in its vaccine, Thorns, however, describes preparing attenuated *M. bovis* strains which are of such low virulence that they only induce small histopathological changes in the mouse mastitis model (FF 23, 24).

As noted above, Thorns expressly teaches that the avirulent strains "should provide further insight into the pathogenesis of *M bovis* mastitis which could perhaps lead to a stable vaccine for this disease" (Thorns 332 (FF 25)). Thus, given these teachings, we agree with the Examiner that an

ordinary artisan preparing an *M. bovis* vaccine with killed cells according to Boothby I would have reasoned that Thorns' attenuated strains would be effective in a similar fashion to the killed cells in a vaccine composition targeting respiratory disease in cows.

We acknowledge, as Appellants argue, that an ordinary artisan might have considered Thorns' "perhaps" language (FF 25) as only a prophetic suggestion of a mastitis vaccine. Claim 56, however, is directed to a vaccine that is protective against respiratory pneumonia, not mastitis.

Given the positive results obtained by Boothby I against respiratory symptoms when using killed *M. bovis* cells as a vaccine (FF 5, 8, 9), and the absence of any clear or direct evidence from Appellants controverting the adequacy of those findings, a preponderance of the evidence supports the Examiner's position that an ordinary artisan would have had a reasonable expectation that Thorns' live, but attenuated, *M. bovis* cells would also function suitably in a vaccine protective against respiratory pneumonia. Thus, as Appellants' arguments do not persuade us that the Examiner failed to make a prima facie case of obviousness with respect to claim 56, we affirm the Examiner's rejection of that claim over Boothby I, Poumarat, and Thorns.

SUMMARY

We affirm the Examiner's rejection of claims 1, 3, 52, 53, and 55 as anticipated by Boothby I.

However, we reverse the Examiner's rejection of claims 5, 6, 29, 30, 40-44, and 54 as anticipated by Boothby I.

We also affirm the Examiner's rejection of claims 1, 3-12, 31-39, and 46-56 as obvious over Boothby I, Poumarat, and Thorns.

However, we reverse the Examiner's rejection of claims 29, 30, and 40-45 as obvious over Boothby I, Poumarat, and Thorns.

TIME PERIOD

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED-IN-PART

cdc

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